American Journal of Hematology 63:68–73 (2000)

Splenic Function in Sickle Cell Anemia Patients in Qatif, Saudi Arabia

Ali H. Al-Jam'a,[1]* Ibrahim A. Al-Dabbous,[2] Sundara Krishna Chirala,[3] Hussain Al-Majid,[4] and Jameela Al-Ali[3]

[1]Internal Medicine Department, Qatif Central Hospital (QCH), Kingdom of Saudi Arabia
[2]Pediatric Department, QCH, Kingdom of Saudi Arabia
[3]Nuclear Medicine Department, Dammam Central Hospital, Kingdom of Saudi Arabia
[4]Radiology Department, King Fahad Hospital of the University, Khobar, Kingdom of Saudi Arabia

A prospective study was conducted to study the splenic function among sickle cell anemia (SCA) patients in Qatif (Eastern Province of Saudi Arabia). Seventy-seven patients (30 children and 47 adults aged 2–57 years) were included. ^{99m}Tc stannous colloid liver–spleen scan was done for each patient during steady state. The splenic function was graded from 0 to 4 in relation to liver uptake. Seventy percent of our patients showed evidence of splenic hypofunction, and most of them (83%) had severe hyposplenism. Up to the age of 4 years, only 17% of the children showed evidence of functional hyposplenism, but by the age of 10 years >50% were hyposplenic. Most of the hyposplenic children had functional hyposplenism, whereas only one-third of hyposplenic adults had autosplenectomy. There was no effect of level of HbF on the frequency of hyposplenism, but on the other hand low MCV seems to be protective against hyposplenism. A significant number of adult SCA patients have clinically enlarged spleens, and almost a third have normally functioning spleens. Because of the low prevalence of hyposplenism in children younger than 4 years of age, routine penicillin prophylaxis is probably not indicated in this population, an issue which needs further evaluation. Am. J. Hematol. 63:68–73, 2000.

Key words: splenic function; functional asplenia; autosplenectomy; sickle cell anemia

INTRODUCTION

The spleen is one of the main organs to be adversely affected in Sickle cell disease (SCD). It is commonly enlarged in early childhood [1], but with time, it undergoes progressive atrophy, due to recurrent perivascular hemorrhage and infarction which reduce the organ to nothing more than a small siderofibrotic vestige [2]. Not only this, but the spleen may lose its function despite its enlargement, a phenomenon known as functional hyposplenia [3]. Asplenia, whether anatomic or functional, exposes these patients, especially children, to fulminant bacterial infections, especially those due to *Streptococcus pneumoniae, Haemophilus influenzae,* and *Salmonella* species [4–8].

Several methods have been used to assess the splenic functions, including the presence of Howell–Jolly bodies in the peripheral blood smear [9], the percentage of circulating pocked red cells [10], and radionuclide scans using ^{99m}Tc sulphur or tin colloid [11].

In Saudi Arabia, there are two different patterns [12,13] of SCD: one in the southwest of the country, which is similar to the African type, and the other in the Eastern Province (EP) (Qatif and Al Hassa Oases), which runs a relatively milder course. The splenic function of patients in EP had been studied before [14–16], but the samples were usually small and the population studied were mostly children.

In this study, we report on the splenic function as assessed but ^{99}Tc-colloid scan in both children and adults with SCA during the steady state. To the best of our

*Correspondence to: Ali H. Al-Jam'a, MD, CABIM, P.O. Box 627, Qatif 31911, Kingdom of Saudi Arabia.

Received for publication 3 January 1997; Accepted 6 October 1999

knowledge, this study is the largest ever reported from this area of Saudi Arabia.

MATERIALS AND METHODS

A prospective study to assess the spleen status in Saudi SCA patients was conducted at Qatif Central Hospital from May 1993 through August 1995. Seventy-seven consecutive SCA patients presenting to the pediatric and adult sickle cell clinics during their steady state were included. There were 30 children (<12 years old) (17 males, 13 females) with age range 2–12 years (mean 7 years) and 47 adults (>12 years old) (30 males, 17 females) with age range 13–57 years (mean 25 years). To ensure homogeneity of the study group, only those patients who were originally from the Eastern Province (EP) of Saudi Arabia (SA) were included.

The diagnosis of SCA was based on criteria described elsewhere [17]. Patients with possible sickle cell β^0 thalassemia (those with microcytosis, and hemoglobin A2 (HbA2) > 4%) were excluded. The definitive diagnosis of associated α thalassemia requires either globin chain analysis or DNA studies, but because these are not available in our hospital, those patients who had microcytosis, normal RDW, and HbA2 < 3.5 [18] were considered to have associated α thalassemia trait. Therefore, the diagnosis of associated α thalassemia made in this way should be interpreted with caution. In all patients, iron deficiency was excluded by the presence of normal transferrin saturation and serum ferritin. The steady state complete blood count was done on a Coulter Counter (Model S-plus, Coulter Electronics Inc., Florida). The reticulocyte count was performed by incubation of patient's EDTA anticoagulated blood with modified brilliant cresyl blue solution, and reticulocytes were counted in 1,000 erythrocytes of the prepared film, by conventional microscopy.

The patients were examined clinically for evidence of hepatosplenomegaly, which was recorded in centimeters below right and left costal margins, respectively, at the midclavicular line. Sonography of the liver and spleen was performed for each patient. The presence, size, and any abnormality of the spleen were noted. The greatest longitudinal axis was taken to represent the size of the spleen. Autosplenectomy was diagnosed by nonvisualization of the splenic tissue or the mere presence of only a very small remnant of splenic tissue. Reticuloendothelial scintigraphy (RES) of the liver and spleen was performed during the steady state after obtaining an informed consent from the patient or his legal guardian. Each patient was given an age- and weight-adjusted dose of ^{99m}Tc stannous colloid (Amerscan Hepatate II) injected intravenously. The splenic uptake of the colloid on the posterior view was classified in relation to the liver uptake into five categories: 0 (no uptake), 1 (markedly decreased), 2 (slightly decreased), 3(equal uptake to liver), and 4 (more uptake than liver) (Figs. 1–5). For the purpose of this study, categories 3 and 4 were considered indicative of normal splenic function, while categories 0,1 and 2 indicate depressed splenic function. A statistical program (Epistat package) was used to perform the various statistical tests [19].

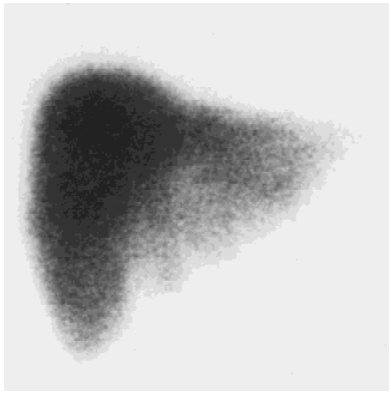

Fig. 1. Liver–spleen scan showing no uptake of the colloid by the spleen: grade "O".

RESULTS

Splenic hypofunction was detected in 54 out of the total 77 patients (70%). Thirty-two of these were adults, and 22 were children. They comprised 68% of adults and 73.3% of children. The difference was not statistically significant. There was no difference in the incidence of hyposplenism between the two sexes in both pediatric and adult age groups (Table I). Hyposplenism appeared as early as 2 years of age. Up to the age of 4 years, only 5 out of the 30 children (16.6%) had evidence of functional hyposplenism, but by the age of 10 years, 15 children (50%) were functionally hyposplenic. Twelve of our patients (10 adults and 2 children) had autosplenectomy on ultrasound evaluation. These patients will of course have no splenic function by isotope evaluation.

Table II shows the distribution of the patients among various grades of splenic function. More than 50% of patients had severe splenic dysfunction (autosplenectomy and grade 0 and 1 of functional hyposplenism). Clinically enlarged spleen was detected in 22 pediatric patients (73.3%) and in 31 adults (66%). The size of spleen ranged from 2 to 14 cm below the left costal margin. More than 90% of the hyposplenic pediatric patients had functional hyposplenism, while in adults about 70% of those with splenic hypofunction had functional hyposplenism (Table III).

Table IV shows the hematological indices in the group with splenic hypofunction as compared to those with normal splenic function. There was no significant differ-

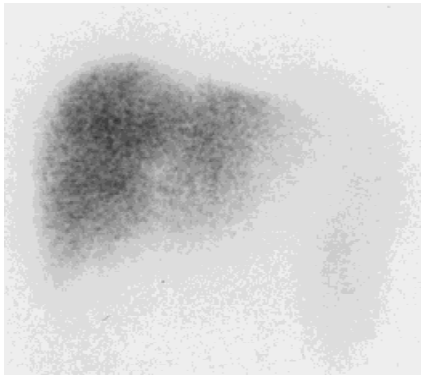

Fig. 2. Liver–spleen scan showing markedly decreased splenic uptake of the colloid: grade "1".

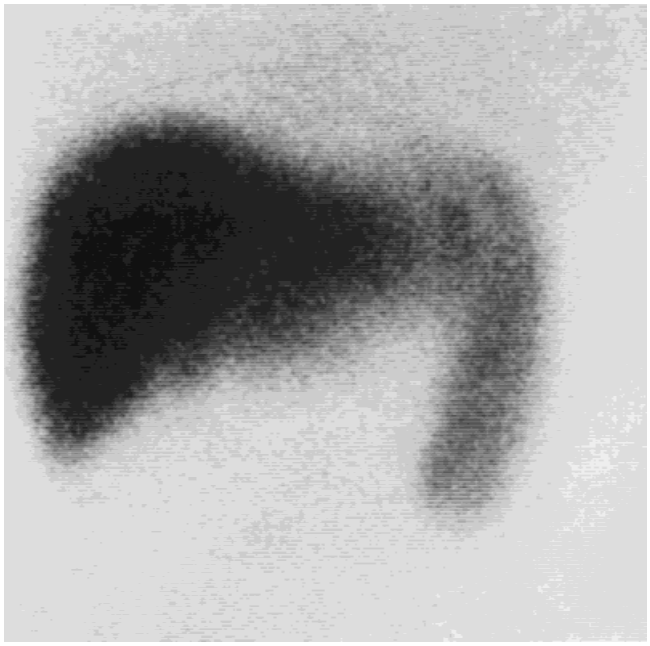

Fig. 3. Liver–spleen scan showing slightly decreased splenic uptake of the colloid: grade "2".

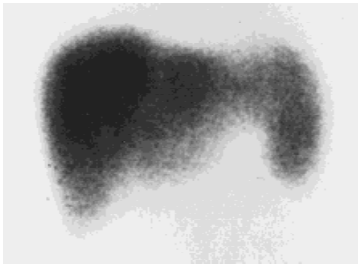

Fig. 4. Liver–spleen scan showing equal uptake of the colloid by the liver and spleen: grade "3".

ence between the two groups in terms of total hemoglobin or hemoglobin F levels. On the other hand, patients with normal splenic function had significantly lower mean corpuscular volume (MCV).

TABLE I. Frequency of Hyposplenism in Relation to Age and Sex of the Patients

	Hyposplenism	Normal splenic function
Adults	32 (19 M : 13 F)	15 (M 11 : 4 F)
Children	22 (13 M : 9 F)	8 (M 4 : 4 F)
	Chi square = 0.005	P Value = 0.8

TABLE II. Distribution of Patients According to the Grade of Splenic Function

	Autosplenectomy	Functional hyposplenia			Normal spl. function		
Age Group		*G0	G1	G2	G3	G4	Total
Pediatric Patients	2**	11	7	4	7	1	30
Adult Patients	10**	14	13	5	7	8	47
Total	12	25	20	9	14	9	77

*G = Grade.
** = These patients are counted in G-0 column.

TABLE III. Frequency of Functional Hyposplenism and Autosplenectomy

	Functional hyposplenism	Autosplenectomy
Adult Patients	22	10
Pediatric Patients	20	2
	Fishers Exact Test P = 0.005	

DISCUSSION

Sickle cell disease in Eastern Province of Saudi Arabia has different clinical and laboratory features when compared to the African SCD. One of the unique features of SCA in the Eastern Province of Saudi Arabia is persisting splenomegaly well into adulthood [13–20]. There are several studies of splenic function in this group of patients [14–16] using either radionuclide studies or the percentage of pocked erythrocytes, but these were conducted on pediatric patients only and the number of patients studied was small. Those reports concluded that splenic function was normal in most of the children with SCD from Eastern Saudi Arabia. Our study, on the other hand, shows different findings than previously reported. We used the ^{99m}Tc colloid liver–spleen scan which is the "gold standard" [21] for the evaluation of splenic function. Seventy percent of our patients had evidence of splenic hypofunction, and more than 50% of them had severe splenic hypofunction. The majority of hyposplenic children and about two-thirds of hyposplenic adults had functional hyposplenism. About a third of the hyposplenic adults had evidence of autosplenectomy. While the frequency of hyposplenism is similar in chil-

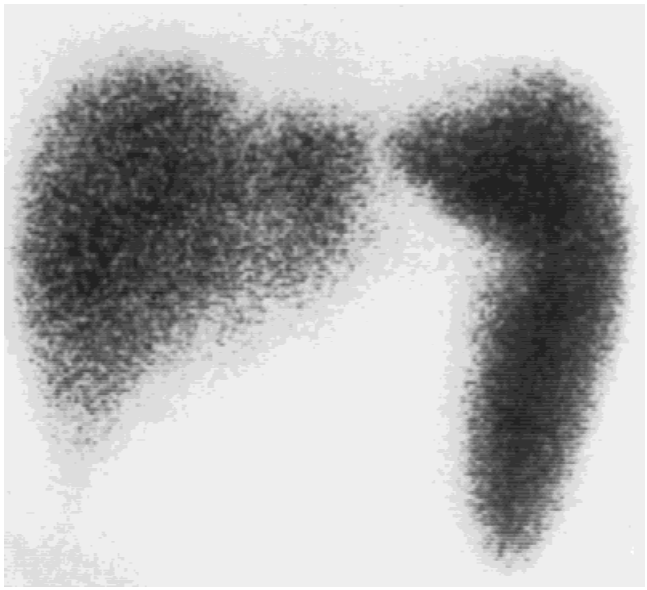

Fig. 5. Liver–spleen scan showing increased splenic uptake of the colloid: grade "4".

dren and adults, the severity of hyposplenism progressed with age, presumably due to repeated splenic infarctions.

In the United States, as many as 90% of children with SS disease will have functional hyposplenism by the age of 3 years [22]. In contrast, our study showed that only 5 patients (17%) below 4 years of age showed evidence of hyposplenism, but by the age of 10 years 50% had hyposplenism. The youngest patient to show functional hyposplenism was 2 years old. We cannot comment on the time of first occurrence of functional hyposplenia because of the small number of patients in this age group.

The spleen has four independent activities [23], including (1) erythrocyte and platelet reservoir, (2) destruction site for damaged erythrocytes, (3) filter for bacteria especially streptococcus pneumonia, and (4) antibody production. Life threatening bacterial infections especially with encapsulated bacteria is a major complication in children with SCD [4–8]. These infections are unusual before the age of 6 months, have a peak incidence in the first 2–3 years of life, and are infrequent after 6 years of age [22]. Asplenia whether functional or anatomic is a major contributing factor for such a complication. In an attempt to overcome this complication, penicillin prophylaxis from 6 months up to the age of 5 years [24] and immunization with polyvalent pneumococcal vaccine, hemophilus influenza type b, and meningococcal vaccines have been suggested [25]. In Eastern Saudi Arabia, *S. pneumoniae* was reported to be the cause of major infections in about 20% of pediatric SCD patients [26,27]. This is a relatively lower frequency than the estimated 600-fold increase in susceptibility to pneumococcal infection in African SCD [5]. These reports coupled with our findings of only 17% of children below 4 years of age having hyposplenism raise doubts about the rational use of penicillin prophylaxis in children with SCD from Eastern Saudi Arabia routinely. Add to this a genuine concern that prolonged penicillin prophylaxis could be harmful during infancy and early childhood as it may impair the development of naturally acquired immunity against *S. pneumoniae* [28]. The other major concern is the likelihood that prophylactic penicillin may be an important factor in the increasing frequency of penicillin-resistant organisms [29]. Further evaluation of the need of penicillin prophylaxis in these patients is required. On the other hand, the use of pneumococcal, hemophilus influenza, and meningococcal vaccines is still advisable. Pneumococcal septicemia was reported in adult SCD patients from Eastern Saudi Arabia [30]. Therefore, the use of pneumococcal vaccine is warranted in adult SCD patients.

The splenic function in Saudi adults with SCA was not previously studied. Our study presents some interesting findings. More than 60% of our patients have a clinically enlarged spleen, and two-thirds of adults with hyposplenism have functional asplenia. The clinically enlarged spleen with depressed reticulo-endothelial (RE) function was documented to be capable of acting as a reservoir for both platelets and erythrocytes [23]. This manifests as chronic hypersplenism and acute recurrent splenic sequestration crises. These manifestations are rare in adult SCA patients of African ancestry but are found more frequently in other variants of SCD such as HbSC disease [23]. Our adult patients are definitely at risk of the above complications, which were reported both in pediatric and adult patients [31–33]. This separation of RE function from the reservoir function presents a challenge to the clinician when faced with evidence of RE dysfunction in an adult with SCD. Could this be an indication for elective splenectomy? A question which is difficult to answer at present. On balance, the decision for splenectomy in an adult with splenic sequestration crisis and depressed splenic function may be easier than that in a child less than 5 years of age with the same clinical problem.

Almost one-third of adults in this study had normally functioning spleens. This is definitely in marked distinction to what occurs in adult SCD patient of African ancestry. This finding supports the overwhelming evidence that SCD in Eastern Saudi Arabia is a different disease from the African type and many of its aspects have to be unraveled.

High levels of HbF was suggested to be protective against some complications of SCD including splenic hypofunction [22,34]. Our study and others [17,35] could not confirm this protective effect. Although there was no statistical difference in the level of HbF among hyposplenic and normosplenic patients in our study, there is no doubt that the generally higher HbF level in patients from Eastern Saudi Arabia (mean HbF of about 20%) is

TABLE IV. Hematological Indices in Patients With Normal and Depressed Splenic Function*

	Total Hb $\overline{X}$ ± SD	HbF $\overline{X}$ ± SD	Platelets $\overline{X}$ + SD	WBC $\overline{X}$ ± SD	MCV $\overline{X}$ ± SD
Hyposplenism	9.4 ± 1.8	20.1 ± 8.4	336 ± 179	9.9 ± 4.5	77.2 ± 9.8
Normal Spleen Function	10.2 ± 1.1	22.3 ± 6.9	238 ± 101	7.5 ± 3.4	71.8 ± 4
P. Value	0.06	0.3	0.01	0.02	0.03

*$\overline{X}$ = mean (Student t-test); SD = Standard Deviation.

contributing to the better splenic function and definitely lower prevalence of autosplenectomy, if compared to African Americans [34]. Patients with microcytosis have better preservation of splenic function than those with normal MCV. α Thalassemia genes are very common in the Eastern Province of Saudi Arabia, approaching a frequency of 0.449 [36,37], therefore most of these microcytic patients are likely to have co-existent α-thalassemia trait. In our study as well as previously reported [16], and a recently reported study [35] the coexistence of α-thalassemia trait is a contributing factor to the preservation of splenic function in SCD from this area.

Our methods can not exclude the presence of $S\beta^0$ thalassemia completely, but we think this will have little if any effect on the results. This is because the frequency of $A\beta^0$ that is found in our population is very low (1.5%) [38], and the pattern of splenic dysfunction in patients with $S\beta^0$ thalassemia was found to be similar to that patients with SCA [22]. Platelet and leukocyte counts were significantly higher in our patients with splenic hypofunction, which is consistent with the concept that thrombocytosis in SCD is caused in part by splenic dysfunction [39].

In conclusion, our study documented the splenic function in adult SCA patients from the Eastern Province of Saudi Arabia and showed a higher frequency of hyposplenism than previously reported in children with SCA especially after the age of 4 years. We admit that this study is a hospital-based one and selection bias of more severely affected patients cannot be denied.

ACKNOWLEDGMENTS

We are indebted to Dr. Adel Al-Khatti, MD, Consultant Hematologist/Oncologist, and Dr. Ahmed H. Al-Salem, Pediatric Surgeon for their meticulous revision of the manuscript. We thank Ms. Luzviminda M. Rosimo for typing the manuscript in its final form.

REFERENCES

1. Serjeant GR. The spleen. In: Sickle cell disease. Oxford: Oxford Medical Publication; 1989. p 109–103.
2. Lukens JN. Hemoglobinopathies S, C, D, E and O and associated diseases. In: Wintrobe's clinical hematology, Indian edition. 9th edition. Bombay: K.M. Varghese Company; 1993. Chap 38, p 1071.
3. Pearson HA, Spencer RP, Cornelius EA. Functional asplenia in sickle cell anemia. N Eng J Med 1969;28:923–926.
4. Robinson MG, Watson RJ. Pneumococcal meningitis in sickle cell anemia. N Eng J Med 1966;274:1006–1008.
5. Barrett Connor E. Bacterial infection and sickle cell anemia. Medicine (Baltimore) 1971;50:97–112.
6. Seeler RA, Jacobs NM. Pyrogenic infection in children with sickle cell hemoglobinopathy. J Pediatr 1977;90:161–162.
7. Overturf GD, Powars D, Baraff LJ, et al. Bacterial meningitis and septicemia in sickle cell disease. AJDC 1977;121:784–787.
8. Adeneyokunno AA, Hendrickse RG. Salmonella osteomyelitis in childhood. Arch Dis Child 1981;55:175–184.
9. Crosby W. Normal function of the spleen relative to red blood cells. Blood 1959;14:399–408.
10. Casper JT, Keethe S, Rodey GE, et al. A new method for studying splenic reticulo endothelial dysfunction in sickle cell disease patients and its clinical application: a brief report. Blood 1976;47:183–188.
11. Marsh GW, Stewart JS. Splenic function in adult coeliac disease. Br J Haematol 1970;19:445–457.
12. Babiker MA, Taha SA. Two different patterns of sickle cell disease in children in Saudi Arabia. Ann Trop Paediatr 1982;2:179–181.
13. Padmos MA, Roberts GT, Sackey K, Kulozik A, Bail S, Morris JS, Serjeant BE, Serjeant GR. Two different forms of homozygous sickle cell disease occur in Saudi Arabia. Br J Haematol 1991;79:93–98.
14. Al Awamy B, Wilson WA, Pearson HA. Splenic fuction in sickle cell disease in Eastern Province of Saudi Arabia. J Pediatr 1984;104:714–717.
15. Mallouh A, Barke GM, Salamah M, Ahmed MS. Splenic function in Saudi children with sickle cell disease. Ann Trop Paediatr 1984;4:87–91.
16. Babiker MA, El-Hazmi MAF, Al Jabori AM, Obeid H, Bahakim HM. Splenic function in children with sickle cell disease. Two different patterns in Saudi Arabia. Scand J Haematol 1985;35:191–193.
17. Al-Jama' AH, Al Dabbous IA. Laboratory diagnosis of patients with sickle cell disease. In: Al-Jama' AH, Al Dabbous IA, editors. Management manual of sickle cell disease, 1st edition. Dammam: Al-Shati Modern Press; 1992. p 264–270.
18. El-Hazmi MAF. Clinical manifestations and laboratory findings of sickle cell anemia in association with α thalassemia in Saudi Arabia. Acta Haematol 1985;74:155–160.
19. Epistat Package. Tracy L. Gustafson, MD, 1705 Gattis School Road, Round Rock, Texas 78664.
20. Perrine RP, Brown MJ, Clegg JB, Weatherall DJ, May A. Benign sickle cell anaemia. Lancet 1972;2:1163–1167.
21. Gaston MH, Reid CD. Infection in sickle cell disease. In: Mankad VN, Moore RB, editors. Sickle cell disease: pathophysiology, diagnosis and management. Westoport, CT: Praeger; 1992. p 271.
22. Pearson HA, Gallagher D, Chileote R, Sullivan E, Williams J, Espeland M, Ritchey AK. Developmental pattern of splenic dysfunction in sickle cell disorders. Pediatrics 1985;76(3):392–397.
23. Powars DR, Pegelow CH. The spleen in sickle cell disease and thalassemia. Am J Pediatr Hematol/Oncol 1979;1(4):343–353.
24. Charache S, Lubin B, Reid CD, editors. Management and therapy of sickle cell disease. Bathesda, MD: NIH Publication No. 85-2117; 1985. Chap 3, p 6.

25. Pearson HA. Sickle cell anemia and severe infections due to encapsulated bacteria. J Infect Dis 1977;136(Suppl):S25–S30.
26. Mallouh AA, Salamah MM. Pattern of bacterial infections in homozygous sickle cell disease. Am J Dis Child 1985;139:820–822.
27. Abusrair HA, Elbashier AM, Al Dabbous IA, Al Khater M. Incidence of major infection in sickle cell pediatric patients at Qatif Central Hospital. Ann S Med 1991;11(3):267–270.
28. Buchanan GR, Sanders JM, Vedro D, Morrison R, Jackson E, Siegel J, Schiffman G. Reduced serum levels of antibody against *Streptococcus pneumoniae* in young children with sickle cell anemia receiving prophylactic penicillin. Blood 1989;74:184a (Abstract Suppl 1).
29. Tan TQ, Mason EQ Jr, Kaplan SL. Penicillin-resistant Systemic pneumococcal infection in children: a retrospective case control study. Pediatrics 1993;92:761.
30. Elbashier AM, Abu-Srair H, Al-Jama' AH, Al Dabbous IA, Malik AG. Septicemia in sickle cell disease patients at Qatif Central Hospital, Saudi Arabia. Saudi Med J 1992;13(3):220–223.
31. Salamah MM, Mallouh AA, Hamdan JA. Acute splenic sequestration in Saudi children with sickle cell disease. Ann Trop Pediatr 1989;9: 115–117.
32. Al Salem AH, Qaisaruddin S, Nasserallah Z, Al Dabbous I, Abusrair H, Al Jama' A. Splenectomy and acute splenic sequestration crises in sickle cell disease. Pediatr Surg Int 1995;11:26–28.
33. Al-Salem AH, Qaisaruddin S, Nasserallah Z, Al-Dabbous I, Al-Jam'a A. Splenectomy in patients with sickle cell disease. Am J Surg 1996; 171:254–258.
34. Al-Awamy BH, Naeem M. Splenic and hepatic function in sickle cell anemia—with special emphasis on patients from the Eastern Province of Saudi Arabia. Saudi Med J 1986;7(5):434–442.
35. Adekile AD, Al Zaabi K, Haider MZ, Tuli M. Molecular and hematological correlates of splenic function among Arab SS patients. Blood 1997;90(10 Suppl 1, Part 2): Abstract No. 2782:21b.
36. Pembrey ME, Weatherall DJ, Clegg JB, Bunch C, Perrine RP. Haemoglobin Bart's in Saudi Arabia. Br J Haematol 1975;29:221–234.
37. El Hazmi MAF. α-Thalassemia in Saudi Arabia: deletion pattern. Hum Genet 1987;76:196–198.
38. Pembrey ME, Perrine RP, Wood WG, Weatherall DJ. Sickle β^0-thalassemia in Eastern Saudi Arabia. Am J Hum Genet 1980;32:26–41.
39. West MS, Wethers D, Smith J, Steinberg M. The Cooperative Study of Sickle Cell Disease: Laboratory profile of sickle cell disease: a cross-sectional analysis. J Clin Epidemiol 1992;45:893.